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PATENT SPECIFICATION

NO DRAWINGS

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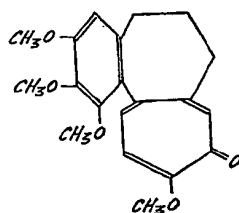
COMPLETE SPECIFICATION

Pharmaceutical and Agricultural preparations comprising Colchicine Derivatives

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

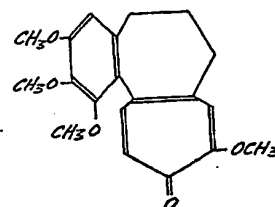
The present invention relates to new pharmaceutical and agricultural preparations comprising colchicine derivatives.

The present invention provides pharmaceutical preparations which comprise des-(acetylamino) - colchicine of the formula (I) or des - (acetylamino) - isocolchicine of the formula (II)



I

and



II

or a mixture of these two compounds as active constituent, in admixture or conjunction with a pharmaceutically suitable carrier, with the exception of a carrier consisting solely of ordinary water or an organic solvent normally used in the preparation of the active ingredient(s), and a process for their manufacture.

The new preparations have a cystostatic and antimitotic effect. They inhibit cell division by preventing the formation of the spindle (metaphase) during the process of nucleus division. They can therefore be used as medicaments in human and veterinary medicine, for example for treating myeloid leukaemia and other types of carcinoma, more especially subacute and chronic manifestations, attacks of gout and rheumatism, or pre-cancerous or cancerous conditions of the skin, for example keratoma senile, epithelium basocellulare or spinocellulare, morbus Bowen or relapses after the X-ray treatment of skin tumours.

The present invention also provides agricultural agents for the production of polyploid

plants, which comprise des - (acetylamino)-colchicine or des - (acetylamino) - isocolchicine or a mixture of these two compounds, in admixture or conjunction with a suitable carrier, with the exception of a carrier consisting solely of ordinary water or an organic solvent normally used in the preparation of the active ingredient(s) and a process for their manufacture.

The preparation of des - (acetylamino)-colchicine and des - (acetylamino) - isocolchicine has been described in *Helv. Chim. Acta* 44, page 540 *et seq.* [1961], but hitherto the physiological action of these compounds has not been known.

Particularly active are those preparations and agents which contain des - (acetylamino)-colchicine as the active ingredient.

The new preparations and agents are made in a known manner, by compounding the active principle with the appropriate carrier. Suitable carriers are organic or inorganic, solid or liquid substances, preferably those that do not react with the active principle. Preferable

[Price 4s. 6d.]

carriers for the pharmaceutical preparations are those which are suitable for enteral, for example oral, parenteral or topical administration, such, for example, as water, alcohol, gelatine, lactose, starches, stearyl alcohol, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, propylene glycol, polyalkylene glycols, white petroleum jelly, cholesterol and/or other known medicinal carriers. The pharmaceutical preparations may be in the form of, for example, tablets, dragees, ointments, creams or capsules, or in a liquid form as solutions, suspensions or emulsions. They may be sterilised and/or may contain auxiliaries, such as preserving, stabilising, wetting or emulsifying agents, solution promoters or salts for regulating the osmotic pressure, or buffers. For use in veterinary medicine the new pharmaceutical preparations may also be admixed with animal fodder, or, alternatively, the animal fodder may form the sole carrier of the preparations.

The pharmaceutical preparations intended for enteral or parenteral use in human or veterinary medicine advantageously contain about 0.01 to 0.5 mg, more especially 0.05 to 0.1 mg, of the active principle per dosage unit.

The amount of carrier may vary within wide limits and depends primarily on the form in which the active substance is administered.

The daily dose depends on the form of administration and on the specific need of the patient; it is easily determined by the attending physician.

For the production of polyploid plants, the agricultural agents may be in, for example, a solid form or in the form of a solution, suspension or emulsion. The conventional carriers may be used, for example water, agar, glycerol and/or lanolin. If desired, the agents may also contain auxiliaries, such as preserving, stabilising, wetting or emulsifying agent. Agents in a liquid form may be used, for example, for spraying the plants. Agents in a salve form can be applied to the plant as they are. According to another method of application, for example, the plant is brushed with a solution containing the active principle or it may be immersed in such a solution. The dosage and the period of time for which the agent is allowed to take effect vary with the way in which it is applied and with the type of plant to be treated. Since, in general, the active principles are less toxic towards plants than towards humans and animals, correspondingly higher doses are permissible.

The following Examples illustrate the invention.

EXAMPLE 1

Tablets containing des - (acetylamino)-colchicine as active ingredient can be prepared in the usual manner from:

	mg	
Des-(acetylamino)-colchicine	0.1	65
lactose	70.9	
gelatine	1.5	
wheat starch	35.	
arrowroot	12	
magnesium stearate	0.2	70
talc	5.3	
total	125.0	

EXAMPLE 2

Tablets containing 0.1 of the dose of the active principle specified in Example 1 can be prepared in the usual manner from:

	mg	
Des-(acetylamino)colchicine	0.01	80
lactose	70.99	
gelatine	1.5	
wheat starch	35	
arrowroot	12	
magnesium stearate	0.2	85
talc	5.3	
total	125.0	

EXAMPLE 3

Des-(acetylamino)-colchicine is made up in the usual manner into an ointment of the following composition:

	grams	
Des-(acetylamino)-colchicine	0.01	90
propylene glycol	10	
sodium lauryl sulphonate	2	
phenyl mercury nitrate	0.002	
cetyl alcohol	15	
water to make	100 grams	95

EXAMPLE 4

An ointment containing less of the active principle than the one described in Example 3 can be prepared, for example, from:

	grams	
Des-(acetylamino)-colchicine	0.001	100
propylene glycol	10	
sodium lauryl sulphonate	2	
phenyl mercury nitrate	0.002	
cetyl alcohol	15	
water to make	100 grams	105

EXAMPLE 5

Tablets containing des-(acetylamino)-isocolchicine as active principle may be prepared in the usual manner from:

5	Des-(acetylamino)-isocolchicine	0.1 mg
	lactose	70.9 mg
	gelatine	1.5 mg
	wheat starch	35.0 mg
	arrowroot	12.0 mg
10	magnesium stearate	0.2 mg
	talc	5.3 mg
		125.0 mg

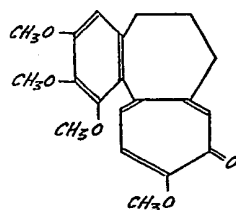
EXAMPLE 6

Des-(acetylamino)-isocolchicine is made up in the usual manner into an ointment of the following composition:

	Des-(acetylamino)isocolchicine	0.01 g
	propylene glycol	10.0 g
	sodium lauryl sulphonate	2.0 g
20	phenyl mercury nitrate	0.002 g
	cetyl alcohol	15.0 g
	water to make	100 g

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation which comprises des-(acetylamino)-colchicine of the formula



in admixture or conjunction with a pharmaceutically suitable carrier, with the exception of a carrier consisting solely of ordinary water or an organic solvent normally used in the preparation of des-(acetylamino)-colchicine.

2. A pharmaceutical preparation which comprises des-(acetylamino)-colchicine or a mixture of des-(acetylamino)-colchicine and des-(acetylamino)-isocolchicine, in admixture or conjunction with a pharmaceutically suitable carrier, with the exception of a carrier consisting solely of ordinary water or an organic solvent normally used in the preparation of the active ingredient(s).

3. A pharmaceutical preparation as claimed in claim 1 or 2, in which the carrier is suitable for topical administration.

4. A pharmaceutical preparation as claimed in claim 1 or 2, in which the carrier is suitable for oral administration.

5. A pharmaceutical preparation as claimed in claim 1 or 2, in which the carrier is suitable for parenteral administration.

6. A pharmaceutical preparation as claimed in any one of claims 1 to 4, in which the carrier is a solid.

7. A pharmaceutical preparation as claimed in any one of claims 1 to 5, in which the carrier is a liquid.

8. A pharmaceutical preparation as claimed in any one of claims 1 to 3, in which the carrier is an ointment base.

9. A pharmaceutical preparation as claimed in any one of claims 4 to 7, which is in unit dosage form and contains 0.01 to 0.5 mg of active principle per dosage unit.

10. A pharmaceutical preparation as claimed in claim 9, containing 0.05 to 0.1 mg of active principle per dosage unit.

11. A pharmaceutical preparation having the composition substantially as described in any one of Examples 1 to 4 herein.

12. A pharmaceutical preparation having the composition substantially as described in Example 5 or 6 herein.

13. An agricultural agent for the production of a polyploid plant, which comprises des-(acetylamino)-colchicine in admixture or conjunction with a suitable carrier, with the exception of a carrier consisting solely of ordinary water or an organic solvent normally used in the preparation of des-(acetylamino)-colchicine.

14. An agricultural agent for the production of a polyploid plant, which comprises des-(acetylamino)-isocolchicine or a mixture of des-(acetylamino)-colchicine and des-(acetylamino)-isocolchicine, in admixture or conjunction with a suitable carrier, with the exception of a carrier consisting solely of ordinary water or an organic solvent normally used in the preparation of the active ingredient(s).

15. An animal feed composition which comprises des-(acetylamino)-colchicine in admixture or conjunction with an animal fodder.

16. An animal feed composition which comprises des-(acetylamino)-isocolchicine or a mixture of des-(acetylamino)-isocolchicine in admixture or conjunction with an animal fodder.

17. A process for the production of a polyploid plant, wherein a plant is treated with an agricultural agent as claimed in claim 13 or 14.

18. A process for the manufacture of a preparation or agent as claimed in any one of claims 1 to 16, wherein the active principle is compounded with the appropriate carrier.

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